

⑪ Publication number: **0 232 932 B1**

EUROPEAN PATENT SPECIFICATION

⑫

④⑤ Date of publication of patent specification:
02.01.91 Bulletin 91/01

⑤① Int. Cl.⁶: **C07D 253/06, C07D 409/10,
A61K 31/53**

②① Application number: **87200088.0**

②② Date of filing: **21.01.87**

⑤④ **5,6-Dihydro-2-(substituted phenyl)-1,2,4-triazine-3,5(2H,4H)-diones.**

The file contains technical information
submitted after the application was filed and
not included in this specification

③① Priority: **30.01.86 GB 8602342**

④③ Date of publication of application:
19.08.87 Bulletin 87/34

④⑤ Publication of the grant of the patent:
02.01.91 Bulletin 91/01

⑤④ Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

⑤⑥ References cited:
**EP-A- 0 154 885
EP-A- 0 170 316
FR-A- 2 231 378
US-A- 3 912 723**

⑦③ Proprietor: **JANSSEN PHARMACEUTICA N.V.**
Turnhoutseweg 30
B-2340 Beerse (BE)

⑦② Inventor: **Boeckx, Gustaaf Maria**
Augustijnenstraat 21
B-2360-Oud-Turnhout (BE)
Inventor: **Raeymaekers, Alfons Herman**
Margaretha
Aanbeeldstraat 1
B-2340-Beerse (BE)
Inventor: **Sipido, Victor**
Winterkoningsstraat 37
B-2060-Marksem (BE)

Best Available Copy

EP 0 232 932 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

EP 0 232 932 B1

Description

2-Phenyl- α -triazine-3,5(2H,4H)-diones and their use for controlling coccidiosis have been described in U.S. Patent No. 3,912,729. The phenyl moiety in the said triazines may, inter alia, be substituted with a benzoyl-, an α -hydroxy-phenylmethyl- and a phenylsulfonyl radical.

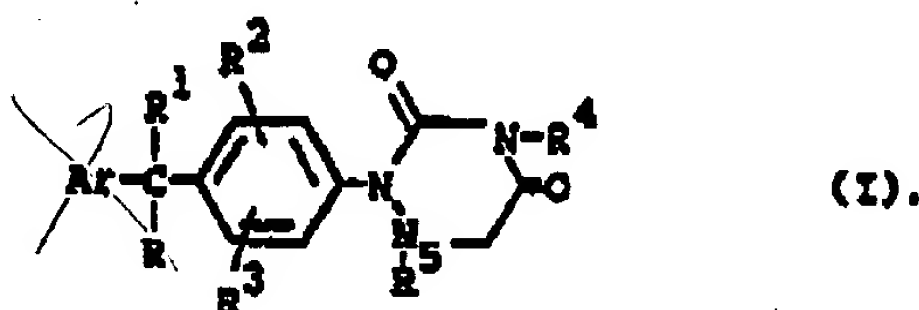
Substituted 2-phenyl-hexahydro-1,2,4-triazine-3,5-diones and their use for combatting Protozoa have been disclosed in Published Eur. Pat. Application No. 0,154,885.

The 5,6-dihydro-2-phenyl-1,2,4-triazine-3,5(2H,4H)-diones, described in the present application, differ from the hereinabove-mentioned triazinones, by the specific substitution of the 2-phenyl moiety, resulting in 5,6-dihydro-1,2,4-triazine-3,5(2H,4H)-diones which are very effective in destructing or preventing the growth of Protozoa in subjects suffering from such Protozoa.

A number of compounds structurally closely related to the ones the present invention are disclosed in EP-A-0 170 316, some of such compounds being excluded by provisions from the definition of the compounds of formula (II-J) as defined hereafter.

Description of the preferred embodiments :

The present invention is related to 5,6-dihydro-2-(substitutedphenyl)-1,2,4-triazine-3,5(2H,4H)-diones having the formula



the pharmaceutically acceptable acid addition, metal or amine substitution salts, and stereochemically isomeric forms thereof, wherein :

Ar is thienyl, halo substituted thienyl, naphthalenyl or a radical of formula



- R is hydrogen, C₁₋₆ alkyl, cyclo C₃₋₆ alkyl, aryl or (aryl)C₁₋₆ alkyl ;
 R¹ is cyano or a radical of formula -C(=X)-Y-R⁹ ;
 said X being O or S,
 Y being O, S, NR¹⁰ or a direct bond ; R⁹ being hydrogen, aryl, C₃₋₆ cycloalkyl or C₁₋₆ alkyl optionally substituted with aryl, hydroxy, amino, mono- and di(C₁₋₆ alkyl)amino, piperidinyl, pyrrolidinyl, 4-morpholinyl, piperazinyl, 4-(C₁₋₆ alkyl)-piperazinyl, 4-(C₁₋₆ alkyl-carbonyl)-piperazinyl, 4-(C₁₋₆ alkylloxycarbonyl)-piperazinyl or 4-((aryl) C₁₋₆ alkyl)-piperazinyl ; and where Y is a direct bond, R⁹ may also be halo ; R¹⁰ is hydrogen, C₁₋₆alkyl or (aryl) C₁₋₆alkyl ; or R⁹ and R¹⁰ taken together with the nitrogen atom bearing said R⁹ and R¹⁰ may form a piperidinyl, pyrrolidinyl, 4-morpholinyl, piperazinyl, 4-(C₁₋₆ alkyl)piperazinyl, 4-(C₁₋₆alkylcarbonyl)-piperazinyl, 4-(C₁₋₆alkylloxycarbonyl)-piperazinyl or a 4-((aryl) C₁₋₆ alkyl)-piperazinyl radical ;
 R², R³, R⁶, R⁷ and R⁸ are each independently hydrogen, halo, trifluoromethyl, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkyloxy, C₁₋₆ alkylcarbonyloxy, mercapto, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl, (trifluoromethyl)-sulfonyl, cyano, nitro, amino, mono- and di(C₁₋₆ alkyl)amino, or (C₁₋₆ alkylcarbonyl)amino ;
 R⁴ and R⁵ are each independently hydrogen, aryl, cyclo C₃₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, (aryl)C₂₋₆ alkenyl or C₁₋₆ alkyl optionally substituted with aryl, hydroxy, amino, mono- and di(C₁₋₆)amino, piperidinyl, pyrrolidinyl, 4-morpholinyl, piperazinyl, 4-(C₁₋₆ alkyl)-piperazinyl, 4-(C₁₋₆ alkylcarbonyl)-piperazinyl, 4-(C₁₋₆ alkylloxycarbonyl)-piperazinyl or 4-((aryl) C₁₋₆ alkyl)-piperazinyl ;
 and R⁶ may also be C₁₋₆ alkylcarbonyl, C₁₋₆ alkylloxycarbonyl, (aryl)C₁₋₆alkylloxycarbonyl or (aryl)carbonyl ;
 wherein aryl is phenyl, optionally substituted with up to two 3 substituents each independently selected from

EP 0 232 932 B1

the group consisting of halo, C₁₋₆ alkyl, C₁₋₆ alkoxy, trifluoromethyl, hydroxy, mercapto, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl, trifluoromethylsulfonyl, cyano, nitro, amino, mono- and di (C₁₋₆ alkyl)amino and (C₁₋₆ alkylcarbonyl)amino.

In the foregoing definitions the term "halo" is generic to fluoro, chloro, bromo and iodo; "C₁₋₆ alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms, such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, butyl, pentyl and hexyl "cyclo C₃₋₆ alkyl" embraces cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; "C₂₋₆ alkenyl" is meant to include straight and branch chained hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms such as, for example, ethenyl, 3-propenyl and 2-butenyl "C₂₋₆ alkynyl" is meant to include straight and branch chained hydrocarbon radicals containing one triple bond and having from 2 to 6 carbon atoms such as, for example, ethynyl, 3-propynyl and 2-butylnyl

Preferred compounds within the invention are those wherein Ar is halothienyl or a radical of formula (a) wherein R⁶ and R⁷ are, each independently, hydrogen, halo, trifluoromethyl, C₁₋₆ alkoxy, hydroxy or C₁₋₆ alkyl; R⁸ is hydrogen; R is hydrogen, C₁₋₆ alkyl, phenyl or halophenyl; R² and R³ are, each independently, hydrogen, halo, trifluoromethyl or C₁₋₆ alkyl; and R⁴ is hydrogen or C₁₋₆ alkyl.

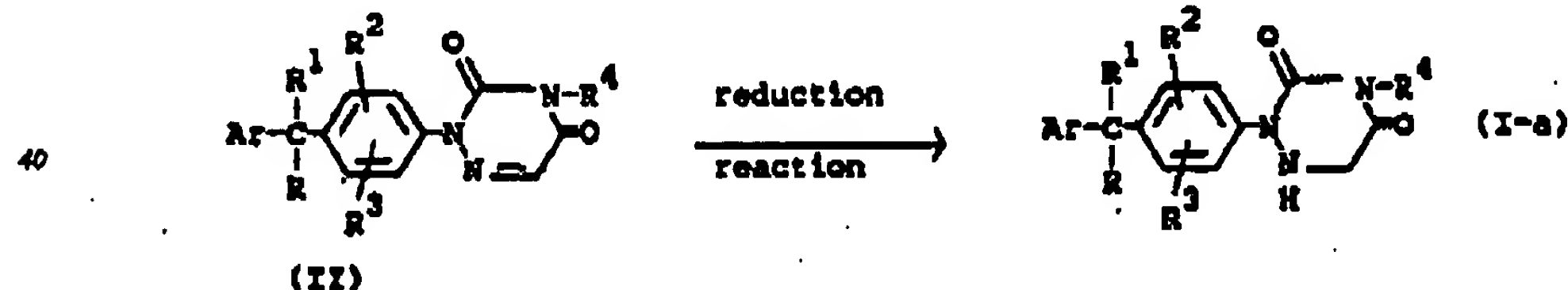
Particularly preferred compounds within the invention are those preferred compounds wherein Ar is a radical of formula (a) wherein R⁶ is halo, R⁷ and R⁸ are hydrogen, R is hydrogen or C₁₋₆ alkyl, R² and R³ independently are halo or hydrogen.

More particularly preferred compounds within the invention are those particularly preferred compounds wherein R⁶ is 4-chloro, R is hydrogen, R² is 2-chloro, R³ is 6-chloro or hydrogen and R⁴ is hydrogen.

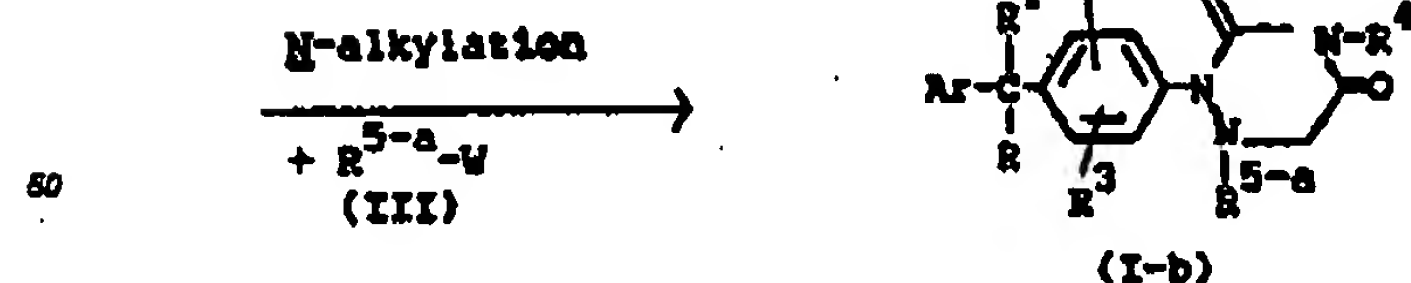
The most preferred compounds within the invention are 2,6-dichloro- α -(4-chlorophenyl)-4-(3,4,5,6-tetrahydro-3,5-dioxo-1,2,4-triazin-2(1H)-yl)benzeneacetonitrile and 2-chloro- α -(4-chlorophenyl)-4-(3,4,5,6-tetrahydro-3,5-dioxo-1,2,4-triazin-2(1H)-yl)benzeneacetonitrile and the pharmaceutically acceptable acid addition, metal or amine substitution salts thereof.

The compounds of formula (I) may conveniently be prepared by a reduction reaction of the corresponding 1,2,4-triazine-3,5-(2H,4H)-dione of formula (II), or an acid-addition salt, metal or amine substitution salt form thereof, thus preparing a compound of formula (I) wherein R⁶ is hydrogen, said compounds being represented by the formula (I-a), and if desired, subsequently reacting the compounds of formula (I-a) with a reagent R^{5-a}-W (III), thus preparing compounds of formula (I), wherein R⁵ is other than hydrogen, said compounds being represented by the formula (I-b). In (III) W represents an appropriate reactive leaving group such as, for example, halo, e.g., chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy or 4-methylphenyl-sulfonyloxy and R^{5-a} has the previously defined meaning of R⁵, provided that it is not hydrogen.

35



45



55

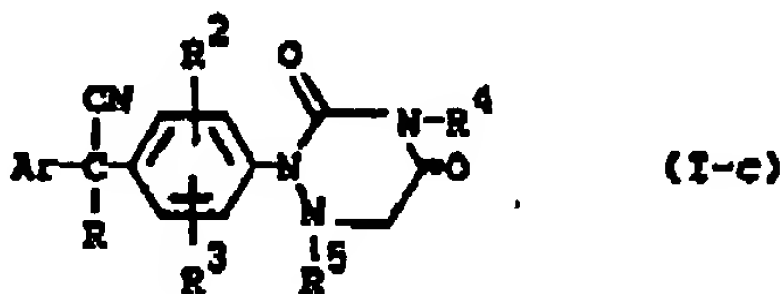
The said reduction reaction is conveniently conducted following art-known procedures for converting a 1,2,4-triazine-3,5-(2H,4H)-dione into a 5,6-dihydro-1,2,4-triazine-3,5-(2H,4H)-dione moiety. A number of such procedures are described in for example the Published Eur. Pat. Application No. 0,154,885 and the references cited therein.

EP 0 232 832 B1

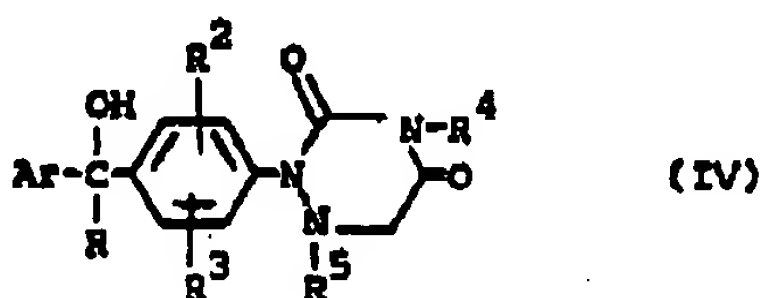
Said reduction reaction may for example be conducted by contacting the starting material of formula (II) with hydrogen in the presence of an appropriate catalyst such as, for example, Raney-nickel, platinum, palladium, platinum(IV) oxide, and the like. Preferably, said reduction reaction is conducted by reacting the starting material (II) with zinc in acetic acid or tin(II) chloride in hydrochloric acid, optionally in the presence of a reaction-inert organic solvent or mixture of such solvents such as, for example, a lower alkanol, e.g. methanol or ethanol; a hydrocarbon, e.g. methylbenzene or dimethylbenzene; a ketone, e.g. 2-propanone, 1-butanone; an ether, e.g. tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, an ester, e.g. ethyl acetate; *N,N*-dimethylformamide, *N,N*-dimethylacetamide; pyridine; acetic acid. Higher temperatures may be used to enhance the reaction rate.

The alkylation reaction of (I-a) with the reagent R^5-W may be conducted following art-known *N*-alkylation procedures. The alkylation reaction is conveniently conducted in an inert organic solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene and dimethylbenzene, a lower alkanol, e.g., methanol, ethanol and 1-butanol, a ketone, e.g., 2-propanone and 4-methyl-2-pentanone, an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane and tetrahydrofuran, *N,N*-dimethylformamide (DMF); *N,N*-dimethylacetamide (DMA); nitrobenzene; dimethyl sulfoxide (DMSO) and 1-methyl-2-pyrrolidinone. The addition of an appropriate base such as, for example, an alkali metal carbonate or hydrogen carbonate, sodium hydride or an organic base such as, for example, *N,N*-diethylethanamine or *N*-(1-methylethyl)-2-propanamine may be utilized to pick up the acid which is liberated during the course of the reaction. In some circumstances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures may enhance the rate of the reaction.

The compounds of formula (I) wherein R^1 is cyano, said compounds being represented by the formula

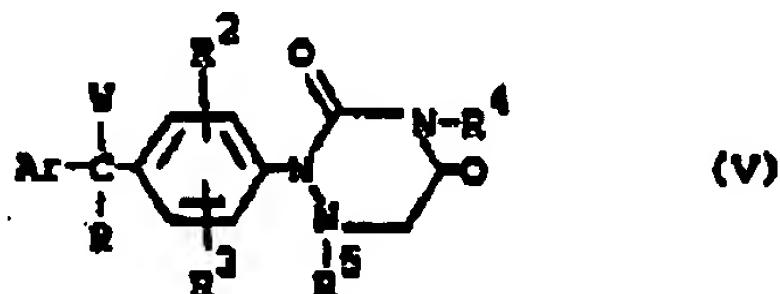


may alternatively be prepared by converting the hydroxy function of a triazinedione of formula



into a nitrile function.

The conversion of (IV) into (I-c) may be effected by art-known procedures. For example, by first converting the hydroxy function into a suitable leaving group and subsequently converting the said leaving group in the thus obtained intermediate having the formula



into a nitrile function.

In (V) W has the meaning of an appropriate reactive leaving group such as, for example, halo, e.g., chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy or 4-methylphenylsulfonyloxy.